AMINOGLYCOSIDE-ASSOCIATED DIZZINESS IN GERIATRIC PATIENTS: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

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ABSTRACT

AMINOGLYCOSIDE-ASSOCIATED DIZZINESS IN GERIATRIC PATIENTS: A PROSPECTIVE OBSERVATIONAL COHORT STUDY. Richard G. Ihnat and Mary E. Tinetti. Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT.

To determine if the elderly have an increased risk of aminoglycoside-induced vestibular damage, 42 subjects over the age of 65 who had received at least five consecutive days of either an aminoglycoside (exposed subjects) or one of a list of control antibiotics (unexposed subjects) were questioned as to the presence of dizziness symptoms after their discharge from the hospital. Laboratory and diagnostic data were also abstracted from their medical records.

Two exposed subjects (13%) and 2 unexposed subjects (8%) reported a new-onset of dizziness since their hospitalization ($p=0.63$). Dizziness increased in severity for 3 (19%) exposed and 2 (8%) unexposed subjects ($p=0.36$). An overall worsening of dizziness was noted in 3 (19%) exposed and 3 (12%) unexposed subjects ($p=0.66$). Although these differences were not statistically significant due to the low power of the study, they indicate a trend may be present. We conclude that an increased risk of dizziness symptoms secondary to aminoglycoside administration has not been proven but may be present and warrants continuation of this study.

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Dedicated to Denise with love ☺

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INTRODUCTION

The aminoglycoside antibiotics have long been known to have significant side-effects which include nephrotoxicity and vestibular and auditory toxicity. Despite their long tenure in our clinical armamentarium, the exact mechanism of their bactericidal and toxic side-effects remains elusive. The elderly are a unique population which may have an increased susceptibility to the toxic side-effects. This pilot study will specifically address the latter issue.

An understanding of the vestibular system is crucial to understanding aminoglycoside toxicity. A review of this system will be followed by discussions of aminoglycoside usage, bacterial toxicity, human toxicities, and how they relate to the elderly.

THE VESTIBULAR SYSTEM

In humans, the vestibular system is responsible for maintaining balance, coordinating eye, head, and body movements, and enabling the eye to fixate on a point while the head is moving. The membranous labyrinth of the middle ear's vestibular apparatus is composed of three semicircular canals, which are oriented in planes 90 degrees apart, and the saccule and the utricle. These structures are housed in the bony labyrinth of the petrous bone and are separated from it by a fluid called perilymph. The semicircular canals supply information about angular acceleration of the head while the utricle provides information about linear acceleration and head position with respect to gravity. The function of the saccule is unknown but is felt to be similar to that of the utricle. The lumens of these structures are connected with each other as well as with the cochlea, and they are filled with a common pool of fluid called endolymph (Kandel & Schwartz, 1985).

The vestibular hair cells are the key sensory cells, and they are located in the ampullae of the semicircular canals and the macula of the utricle. On its luminal membrane, each hair cell has one kinocilium and several stereocilia which project into the endolymph. These projections are oriented along the cell membrane so that the kinocilium is lateral to the stereocilia. When the head accelerates, the viscous endolymph lags behind which causes it to move relative to the hair cells of the semicircular canals. When the force of the fluid bends the stereocilia towards the kinocilium, the cell depolarizes. When they bend away from the kinocilium, the hair cell hyperpolarizes. In this manner, variations from the hair cell's baseline rate of 15 impulses per second code for the direction of the movement. The number of cells recruited delineates the magnitude of the acceleration (Kandel & Schwartz, 1985).

The utricle works in a manner analogous to the semicircular canals, but motion of tiny crystals called otolith, which are embedded in a gelatinous matrix, is substituted for the motion of the endolymph. The otolith are composed of calcium carbonate and rest on the hair cell cilia. With the head in anatomical position, the macula of the utricle is in the horizontal plane. As the force of gravity acts on the otolith which rest on the stereocilia, the cilia are bent causing them to either hyperpolarize or depolarize depending on the head's orientation to gravity (Kandel & Schwartz, 1985).

Impulses from the hair cells of the canals and utricle are transmitted to bipolar cells in the vestibular ganglia of the eighth nerve where the data is integrated to provide information about the position and motion of the head. Much of this data is transmitted into the cerebellum, median longitudinal

fasciculus, reticular formation, and spinal cord and thus remains predominantly in the unconscious realm. In concert with information provided by the other senses, vestibular input is crucial for movement and balance.

When any part of the vestibular system breaks down, dizziness, nausea, and ataxia result. The hair cells, which are one of the key components, are vulnerable to a wide variety of insults, among which are the toxic effects of drugs. This study investigated the effects of the aminoglycoside antibiotics on the vestibular system in elderly patients.

Of the several tests used to determine if the vestibular system is intact, the thermal test and the Romberg test are the most common. In the thermal test, either warm or cold water is dropped into the external acoustic meatus to simulate acceleration. This local change in temperature sets up convection currents in the endolymph which causes the fluid to move and influence the hair cells. In the normal individual, this results in nystagmus. If nystagmus is depressed or eliminated, it indicates the presence of vestibular dysfunction. The Romberg test evaluates the utricle testing the subjects ability to maintain balance when deprived of visual cues.

These tests, however, are somewhat insensitive, and it is difficult to quantitate the degree of vestibular dysfunction. Dizziness, being the clinical manifestation of vestibular dysfunction, is likewise difficult to assess or quantitate. Thus, dizziness is largely a subjective experience which can be reported but not satisfactorily tested. Consequently, this study focused on subjective reporting of dizziness as a measure of outcome.

AMINOGLYCOSIDES

Aminoglycoside antibiotics are derived from the soil actinomycetes Streptomyces and Micromonospora, and they were first discovered by Selman Waksman's group at Rutgers University in 1944 (Schatz et al., 1944). The aminoglycosides are stable, hydrophilic, polycationic amino sugars bound in a glycosidic linkage to a central hexose sugar. For systemic administration, they must be administered parenterally secondary to poor oral absorption, and their polycationic structure is the basis for their poor central nervous system penetration. They are distributed predominantly in the extracellular space compartment, and they are excreted unmetabolized by the kidney with a half-life of about two hours. The antimicrobial effects of gentamicin, tobramycin, and netilmicin are usually achieved at peak serum concentrations of 4-8 mcgs/ml, and kanamycin is effective at 15-40 mcgs/ml. Streptomycin and amikacin are efficacious at 20-30 mcgs/ml. Aminoglycosides kill in a concentration-dependent manner. The higher the concentration, the faster the bacteria are killed (Lampe, 1986; Gilman, 1985).

Clinically, the most commonly used aminoglycosides are streptomycin, kanamycin (Kantrex, Kebcil), neomycin (Mycifradin, Neobotic), gentamicin (Garamycin), tobramycin (Nebcin), amikacin (Amikin), netilmicin (Netromycin), paromycin (Humatin), dibekacin, and sisomicin (Siseptin). As a class, single-agent aminoglycoside therapy is primarily used against aerobic gram-negative bacilli (Lampe, 1986; Gilman et al., 1985). The aminoglycosides are also commonly used in combination with other antibiotics with which they act synergistically. Such combinations typically include cell wall inhibitors,

such as beta-lactams or vancomycin, which are believed to damage the peptidoglycan cell wall and allow the aminoglycosides easier access to the bacterial cytoplasm (Plotz & Davis, 1962). This is done in serious infections such as bacteremia, peritonitis, nosocomial pneumonia, osteomyelitis, septic arthritis, burns, pyelonephritis, and meningitis where gram-negative bacilli are either proven or suspected (John, 1988; Lampe, 1986 & Gilman et al., 1985). Of particular concern is *Pseudomonas aeruginosa* coverage. Gentamicin, tobramycin, and amikacin are particularly effective in this regard.

MECHANISM IN BACTERIA

There are significant pharmacokinetic differences among the aminoglycosides, and they may therefore have different methods of transport and action (Taber et al., 1987; Arrow & Taber, 1986). As a class, unlike the penicillin and cephalosporins, they must enter the bacteria in order to be bactericidal. The bacterial capsule (when present), outer membrane, and cell wall do not seem to be a significant impediment to penetration (Taber et al., 1987; Miller et al., 1986; Peterson et al., 1985; Nichols & Slack; Nakae & Nakae, 1982). It is interesting to note, however, that the proposed mechanism for the synergy between beta-lactams and aminoglycosides is that the beta-lactam damages this wall and allows the aminoglycosides easier access to the cytoplasm (Miller et al., 1986; Plotz & Davis, 1962). Therefore, if the cell wall is not a significant barrier, a new explanation for this synergy must be sought.

The process by which aminoglycosides cross the inner membrane has engendered the greatest controversy. Bryan & Van Den Elzen (1976) proposed

an overview of the process in which aminoglycoside uptake is divided into three phases. The first phase involves ionic binding to the inner membrane in an energy-independent manner. In gram-negative bacteria, they would bind to lipopolysaccharides, phospholipids, and outer membrane proteins while in gram-positive bacteria, they would bind to phospholipids and teichoic acids (Taber et al., 1987). In energy-dependent phase I (EDPI) the positively charged aminoglycosides associate with membrane "transporters" and small amounts are shuttled across the membrane traveling down the electrical potential energy gradient to the relatively negatively charged interior of the cell. The slow leak of aminoglycoside into the cell during EDPI may occur at zones of growth or through faulty protein channels which may normally exist in nature (Davis et al., 1986).

After small quantities of drug have entered the cell during EDPI and have bound to ribosomes, energy-dependent phase II (EDPII) begins and allows more rapid entry of large amounts of antibiotics into the cells (Bryan & Van Den Elzen, 1976). Once inside the cell, the aminoglycosides bind almost irreversibly to the 30S ribosomal subunit to create a nonfunctional complex which blocks initiation of runoff (free) ribosomes and causes misreading of the genetic code in polysomes. Irreversible binding to ribosomes and subsequent loss of protein synthesis is probably at least part of the mechanism for bacterial cell death (Taber et al., 1987).

Membrane potential (Mates et al., 1983; Miller et al., 1980), active electron transport (Arrow & Taber, 1986; Campbell et al., 1980), and functioning ribosomes (Taber et al., 1987; Muir et al., 1984; Davis, 1982) are

necessary for the rapid uptake of aminoglycosides during EDPII. These factors may be related through the functioning of the ATP synthase molecule. Normally, this enzyme produces ATP when the proton motive force overcomes a threshold value. Alternatively, the enzyme can consume ATP to create a proton motive force. After working with *E. coli* mutants possessing various combinations of functional and non-functional components of the enzyme, Humbert and Altendorf (1989) proposed that inactive enzymes would allow proton motive force, and therefore membrane potential, to rise and reach a threshold level required for aminoglycoside uptake without converting the proton motive force into ATP. On the other hand, dysfunctional enzymes which act as proton pores lower the proton motive force, and hence the membrane potential, below the threshold limit for aminoglycoside uptake.

This understanding can be used to construct a model of aminoglycoside entry. After small quantities of aminoglycoside have entered the cell during EDPI and altered protein synthesis (Davis et al., 1986), inactive ATP synthase would be produced. Under conditions of active electron transport, the membrane potential would rise. Since the inactive ATP synthase could not convert the membrane potential to ATP, it would rise uncontrollably. The elevated membrane potential would then drive aminoglycoside molecules through other pores created by faulty RNA translation.

The human mitochondria shares some similarities with bacterial cells in that it has an electron transport chain and bacteria-like ribosomes. Nevertheless, it is unclear which, if any, of the steps in bacterial cell death are common to human toxicity.

TOXICITY

The side effects of the aminoglycosides, which have a low therapeutic/toxic ratio compared to other antibiotics, are well-known. Ototoxicity, nephrotoxicity, neuromuscular blockade, skin rash, drug fever, gastrointestinal upset, malabsorption, blood dyscrasias, transaminitis, retinal damage, and peripheral neuropathies have all been described (Judson, 1989; Edson & Terrell, 1987; Lampe, 1986 & Gilman, et al., 1985). The clinical practice of measuring serum peak and trough levels of the aminoglycosides is an attempt to avoid subjecting patients to unnecessarily high doses of these drugs in the hope of minimizing the side effects. There are also several significant drug interactions which must be considered. Nephrotoxicity can be produced by concurrent administration of methoxyflurane (Penthrane), amphotericin B (Fungizone), vancomycin, cisplatin (Platinol), cyclosporine (Sandimmune), indomethacin (Indocin IV), cephalothin (Keflin), cephaloridine, and loop diuretics such as furosemide (Lasix), bumetanide (Bumex), and ethacrynic acid. Additionally, neuromuscular blockade has been reported when succinylcholine (Anectine, Quelicin, Sucostrin) or tubocurarine were used concomitantly with aminoglycosides (Lampe, 1986). Furthermore, in the guinea pig, Brummett (1981) demonstrated that concurrent use of loop diuretics and aminoglycosides results in significantly enhanced ototoxicity.

Of the aminoglycoside side-effects nephrotoxicity and ototoxicity are the most common. The term ototoxicity encompasses both auditory and vestibular toxicity. Of these three side-effects, vestibular damage is the most difficult to

measure and quantitate. Perhaps for this reason, most of the work in the scientific literature has focused on renal and auditory toxicity.

NEPHROTOXICITY

The effect of aminoglycosides on the kidney has been extensively studied, and the incidence of nephrotoxicity is estimated to be 3-26% of all patients (Smith et al., 1980; Appel & Neu, 1977). Risk factors include hypotension, hypovolemia, advanced age, obesity, recent prior aminoglycoside therapy, duration of treatment, preexisting renal insufficiency, and elevated serum drug levels (Appel, 1990; Corcovan et al., 1989; Edson & Terrell, 1987; Lampe, 1986; Cabrera et al., 1982).

Aminoglycoside nephrotoxicity begins with proteinuria, enzymuria and cylinduria. There is a decrease in GFR which leads to elevated BUN and serum creatinine levels and the onset of usually nonoliguric failure seven to ten days into therapy (Appel, 1990). These effects are reversible and cumulative (Edson & Terrell, 1987).

Houghton's group (1988) administered subtherapeutic doses of gentamicin to rats so that the serum levels were either low or unmeasurable for a period of six months and found that their kidneys progressed from mild chronic tubulointerstitial nephritis to progressive renal failure. Although aminoglycosides would never be given in this fashion, it suggests that even assiduous attention to peak and trough levels might still result in some renal disease.

The rat is an excellent model of nephrotoxicity, and Silverblatt (1982) and Appel (1990) summarized this work. After binding to phospholipid receptors on the brush border of the tubular cells, gentamicin is reabsorbed from the glomerular filtrate mainly in the proximal tubule by pinocytosis and stored in lysosomes. Some also remains in the cytoplasm (Wedeen et al., 1983). Lysosomal storage accounts for the relatively high concentration found in renal cortex and may involve irreversible binding to various cellular constituents (Oshima et al., 1989). Gentamicin is then excreted into the urine by reverse endocytosis and enjoys a half-life of seven days. While in the lysosome, high concentrations of gentamicin cause the membrane to become leaky and inhibit the degradation of complex lipids. As these lipids build up, they form the myeloid bodies which are seen with electron microscopy. Gentamicin also damages the mitochondria which in turn leads to a depletion of ATP (Simmons et al., 1980) and changes in subcellular calcium compartmentalization. Other cellular changes include an inhibition of the Na/K ATPase (Lipsky & Lietman, 1980) and a decrease in apical membrane marker enzymes levels (Inui et al., 1988). Once proximal tubule cell damage occurs, it is "translated" into a declining GFR possibly through vasoconstrictive hormones or backleak of waste across the damaged epithelium. It is difficult to discern which changes are significant and which are merely epiphenomena. It is also difficult to determine which effects are common to the mechanism of hair cell death seen in ototoxicity since the research literature on this subject is sparse.

OTOTOXICITY

Aminoglycoside ototoxicity involves irreversible, dose-related damage to the hair cells of the cochlea and vestibular apparatuses of the inner ear. Auditory toxicity is conventionally taken to mean at least a 15dB decrease in hearing acuity in the range from 250-8,000 Hz, and vestibular toxicity is a loss of nystagmus in the thermal test. The human attack rate for auditory toxicity, with gentamicin and tobramycin, is 10-11% (Smith et al., 1980). Brummett & Morrison (1990), however, used the same criteria on a group of healthy volunteers who were not receiving any medications and found that 20-33% of the subjects met the criteria for new-onset auditory toxicity during the course of study. They concluded that the incidence of this complication was probably overrated.

Since most large studies have focused on auditory damage as a measure of aminoglycoside ototoxicity, it is difficult to obtain reliable estimates for vestibular toxicity. Estimates from some of the larger studies of the rate in the general population range from 0.4% - 2.5% for most of the aminoglycosides (Arcieri et al. 1970; Neu & Bendush, 1976), but with streptomycin, the estimate is close to 20% (Wilson et al., 1984)[Table 1]. Of the aminoglycosides, kanamycin, neomycin, and amikacin primarily affect hearing while gentamicin and streptomycin seem to chiefly affect the vestibular system. Tobramycin seems to cause both types of ototoxicity equally (Edson & Terrell, 1987; Lampe, 1986; Gilman et al., 1985).

Clinically, patients with auditory toxicity often complain of tinnitus or a sense of "fullness" in their ears, but by that point there may already be

TABLE 1

AMINOGLYCOSIDE TOXICITY RATES

AGENT	N	AUDITORY	VESTIBULAR	CITATION
gentamicin	34	N/E	10.0%	Nordstrom et al., 1973
	1484	2.3%	2.5%	Jackson & Arcieri, 1971
	1327	1.3%	2.0%	Arcieri et al., 1970
	26	3.8%	3.8%	Lerner et al., 1977
	45	0.0%	16.0%	Tjernstrom et al., 1973
	40	7.5%	23.0%	Meyers, 1970 *
	181	N/E	2.2%	Waisbren, 1969
	138	16.0%	15.0%	Fee, 1980
streptomycin	36	N/E	19.0%	Wilson et al., 1984.
tobramycin	138	15.0%	4.6%	Fee, 1980
	3506	0.3%	0.4%	Neu & Bendush, 1976
amikacin	1548	4.6%	0.7%	Lane et al., 1977
	27	7.4%	0.0%	Lerner et al., 1977
	55	24.0%	0.0%	Black et al., 1976
kanamycin	81	24.0%	9.9%	Finegold et al., 1958

N/E = Not Evaluated

* = dosage not adjusted for renal insufficiency

permanent high frequency hearing loss (Lampe, 1986). Vestibular damage is often manifest by a moderate head ache in the early stage lasting 1-2 days. This is followed by 1-2 weeks of nausea, vomiting, vertigo, dizziness, an inability to perceive termination of movement ("mental past pointing"), difficulty focusing and reading, a positive Romberg test, and nystagmus. The chronic phase begins suddenly and is heralded by ataxia and lasts for two months. The compensatory stage in which the patient learns to adapt using visual cues follows gradually until the symptoms only become apparent when the eyes are closed. In cases where the damage is not permanent, this recuperation may take more than a year, and recovery is less satisfactory in older patients (Gilman et al., 1985; Neu & Bendush, 1976). Moreover, the onset is variable and can be quite rapid. Miyoshi(1988) examined patients with tuberculosis or urological infections and found that some had their first symptoms after less than five days of treatment. Others have reported a delayed response in which the symptoms don't appear until several weeks after the drugs are discontinued (Neu & Bendush, 1976).

MECHANISM IN HUMANS

The exact mechanism of vestibular hair cell injury and how it relates to the nephrotoxic or bactericidal mechanisms discussed previously is still not clear. Much of the work has been done on the hair cells of the organ of Corti, but since aminoglycosides seem to damage both vestibular and auditory hair cells, the results are probably applicable to both. Some of the renal data may also be applicable.

That the aminoglycosides damage hair cells is clear. Animal studies have demonstrated that lesions occur at both the inner hair cells of the organ of Corti and the vestibular hair cells (Theopold, 1977; Wersall et al., 1973; McGee et al., 1969; Koide et al., 1966; Duvall & Wersall 1964). The results of these studies also show the eighth nerve to be spared. Huizing & de Groot (1987) reviewed the human data and determined that in the cochlea, outer hair cells are affected first before the inner hair cells. The stria vascularis is also injured. Finally, the supporting structures and nerves rapidly degenerate secondary to hair cell loss and not due to direct drug toxicity. They did not look at the vestibular hair cells.

The highest concentrations of aminoglycosides in the body occur in the endolymph, perilymph, and kidney - the areas where toxicity is the greatest. Federspil, et al. (1976) examined the perilymph of guinea pigs after a subcutaneous bolus injection of aminoglycoside and found that the drug concentration in the perilymph rose gradually bilaterally until it was equal to that of the serum. Beyond that point, the serum concentration began to drop quite precipitously, but levels in the perilymph decreased very slowly. Indeed, after 5 hours the aminoglycoside concentration in the middle ear was much higher than in brain, heart, and liver. From their data, they were able to calculate the perilymph half-lives for gentamicin (12 hours), tobramycin (11 hours), and amikacin (10 hours).

This accumulation is also seen in rats, where Huy et al. (1983) detected gentamicin in the endolymph up to 15 days after administration of the drug was discontinued. Whereas the serum half-life of gentamicin in the rat is only

40 minutes, they were unable to even calculate the half-life in the endolymph. In humans, the half-lives of the aminoglycosides in the endolymph are up to four times greater than the serum half-lives (Neu & Bendush 1976). The exact clinical significance of this is unclear, but this prolonged exposure may impair the ability of the cells to maintain the proper cation concentrations in the endolymph and thus may lead to reversible ototoxicity (Neu & Bendush 1976). This effect can be quite rapid. Direct injection of aminoglycoside into guinea pig endolymph produces an immediate suppression of cochlear function (Konishi, 1979). Wilson & Ramsden (1977) obtained similar results in humans with systemic bolus administration, and they noted the effects to be rapid and reversible. They suspected this rapidity ruled out interruption of protein synthesis as a possible mechanism. Rather, they speculated that toxicity was due to interference with energy metabolism or cation transport. Permanent ototoxicity due to cell death would then result from either the long-term loss of these gradients or to direct toxic effects on hair cells by the aminoglycosides.

Early theories as to the mechanism of the toxic side-effects implicated the ribosomes (Spoendlin, 1966) or the cell membrane (Wersall & Flock, 1964). Many of the current theories have focused on phospatidyl inositol (PI) metabolism. The PI cycle is an important second messenger system which is known to be activated by gonadotropin releasing hormone and vasopressin and is part of the alpha-one adrenergic receptor in liver tissue (Patton et al., 1989; Zubay, 1983). Moreover, it is activated in platelet by thrombin and collagen to promote platelet aggregation (Polascik, 1987). When these cell membrane receptors are occupied, phospholipase C (PLC) cleaves PI into diacylglycerol

(DG) and inositol 1,4,5 triphosphate (IP_3). IP_3 liberates calcium from the endoplasmic reticulum until it is degraded to inositol. DG, in the presence of the calcium liberated by IP_3, activates membrane-bound kinase C. Kinase C phosphorylates various cellular proteins and thus may control cellular division. DG is then phosphorylated to become phosphatidic acid (PA). After PA combines with cytosine triphosphate and inositol, IP_3 is regenerated and the cycle may begin again (Patton, 1989). An alternative pathway involves the action of diacylglycerol lipase upon PA to form arachidonic acid, the precursor to prostaglandin synthesis (Zubay, 1983).

Interest in PI metabolism as the molecular site of injury in aminoglycoside toxicity began when Schacht (1976) took subcellular fragments of guinea pig cerebral cortex and found that neomycin bound to the polyphosphoinositide component. Polyphosphoinositides are found in the highest concentrations in neural tissue (Hauser & Eichberg, 1973). Schacht speculated that by binding to it, neomycin may block polyphosphoinositide from acting as a substrate for phosphorylation and thus interfere with membrane function. Lodhi and associates (1979) duplicated this work by demonstrating that neomycin binds to an artificial monomolecular membrane of polyphosphoinositide. In addition, they found that it displaced calcium from the membrane. From this observation, they postulated that neomycin may act by blocking calcium that is necessary for membrane function.

Furthermore, it is known that aminoglycosides competitively inhibit renal cytoplasmic PLC, possibly due to their structural similarity to PI (Lipsky

& Lietman, 1982). Not only would this alter the response of the second messenger system, but also it would increase the concentration of PI.

Renal phospholipase A (PLA), which degrades neutral lipids, is synergistically inhibited by aminoglycosides and PI (Hostetler & Jellison, 1990). Hostetler & Jellison (1990) proposed that the aminoglycosides bind to PI, which is not normally a substrate of PLA, to create a new conformation which prevents PLA from interacting with its usual substrate. Clearly, aminoglycoside inhibition of PLC would lead to an accumulation of PI and subsequently inhibition of PLA. This chain reaction might then cause a build-up of neutral phospholipids and myeloid body formation.

Support for this hypothesis comes from lipid analysis of membranes in renal cells treated with aminoglycosides. Feldman and coworkers (1982) found that the increase in PI concentration was an early effect and hence may be part of the pathogenesis. Since aminoglycosides are known to bind with PI at the apical membrane, they postulated that it might also be related to uptake. PI, though, is not one of the predominant lipids in myeloid body formation in fibroblasts (Oshima et al., 1989). Rather, phosphatidyl choline, bis-(monoacylglycerol) phosphate, and phosphatidylserine show the greatest increase. Oshima's group (1989) further suggested that actual myeloid body formation may not be the cytotoxic mechanism, but rather, cytotoxicity may result from aminoglycoside binding to organelles other than lysosomes.

PI is located on the inner leaflet of the cell membrane, so clearly, to affect these molecules, aminoglycosides must somehow enter the cytoplasm of the hair cells. There is evidence that this occurs early during exposure to

aminoglycosides (Wedeen et al., 1983). In fact, aminoglycoside sequestration in the lysosome may even be an adaptive response to protect the cell from damage (Williams et al., 1984; Wedeen et al, 1983).

Simmons and associates (1980) found that mitochondria of rat kidneys treated with gentamicin had decreased cellular respiration, and the cells had less ATP than controls. The parallel with bacterial cytochrome systems is inescapable. It would be reasonable to presume that the inhibition of Na/K ATPase seen in renal cells might also apply to hair cells. For a hair cell which depends on membrane potential for its function, this inhibition might also affect cell viability. Other intracellular aminoglycoside effects would include inhibition of protein kinase C (Hagiwara et al., 1988) and stimulation of messenger-independent protein kinases (Ahmed et al., 1988).

It is unclear which of these observations are related to the actual mechanism of cytotoxicity and which are epiphenomena. It does seem, however, that PI metabolism is a crucial factor. Further research needs to be done to discover exactly how these compounds affect bacteria and how it relates to hair cell death and other side-effects.

RISK FACTORS

In the various studies of the ototoxic effects of the aminoglycoside antibiotics, several factors have been identified which seem to be correlated with increased risk of vestibular damage [Table 2]. Renal insufficiency (especially when aminoglycoside dosage is not adjusted accordingly), high serum concentrations of the drug, duration of therapy, and previous treatment

with aminoglycosides have been noted as factors by multiple authors (Edson & Terrell, 1987; Arcieri et al., 1970; Jackson & Arcieri, 1971; and Wilson et al., 1984; Nordstrom et al., 1973). Obesity, preexisting auditory impairment, bacteremia, dehydration, and poor liver function have also been implicated (Gilman et al., 1985).

In their work on aminoglycoside side-effects, Moore and associates (1984) surveyed 135 patients who had received at least 9 doses of aminoglycoside antibiotics. They found total dose, duration of therapy, peak temperature, bacteremia, liver dysfunction, and dehydration to be risk factors for hearing loss. To explain some of these results, they speculated that if prostaglandin E is cytoprotective against the effects of bacterial endotoxins or leukocyte pyrogen on the hair cells, then aminoglycosides might be indirectly responsible by blocking PLC (Lipsky & Lietman, 1982). PLC cleaves DG from PI which can serve as a precursor of arachidonic acid and eventually prostaglandin E (Zubay, 1983). Furthermore, they postulated that the increased risk in those with liver dysfunction might somehow be related to CNS depression seen in liver failure. They were unable to correlate hearing loss with hematocrit, age, bicarbonate concentration, sex, presence of urinary tract infection or pneumonia, prognosis, or use of clindamycin, cephalothin, or furosemide. They did not examine vestibular toxicity.

Another potential risk factor is poor nutrition. In guinea pigs that were food-restricted (but received water ad lib), Prazma and coworkers (1983) noted enhanced hair cell death in those subjects that received tobramycin or gentamicin. They elicited no altered serum pharmacokinetics, and suggested

TABLE 2
AMINOGLYCOSIDE OTOTOXICITY RISK FACTORS

RISK FACTOR	TOXICITY*	MODEL**	CITATION
renal insufficiency	V	H	Nordstrom et al., 1973
	V,A	H	Finegold et al., 1958
	V	H	Tjernstrom et al.,1973
	A	H	Fee, 1980
	V,A	H	Neu & Bendush, 1976
prior treatment	V,A	H	Edson & Terrell, 1987
	V	H	Wilson et al., 1984
	V	H	Tjernstrom et al.,1973
high serum concen.	V,A	H	Edson & Terrell, 1987
	V	H	Wilson et al., 1984
	V	H	Nordstrom et al., 1973
	V,A	H	Finegold et al., 1958
treatment duration	V	H	Nordstrom et al, 1973
	A	H	Moore et al., 1984
high temperature	A	H	Fee, 1980
	A	H	Moore et al., 1984
	A	A	Henry et al., 1983
semistarvation	A	A	Prazma et al., 1983
noise	A	A	Brown et al., 1980
	A	A	Jauhiainen et al.,1978
liver dysfunction	A	H	Moore et al., 1984
bacteremia	A	H	Moore et al., 1984
dehydration	A	H	Moore et al., 1984
total dose	A	H	Moore et al., 1984
auditory dysfunct	V	H	Tjernstrom et al.,1973
hematocrit	V	H	Fee, 1980
other drugs	V,A	H	Neu & Bendush, 1976

* vestibular toxicity = V, auditory toxicity = A
** human data = H, animal data = A
auditory dysfunct = a history of preexisting auditory dysfunction.
other drugs = concomitant use of other ototoxic drugs such as furosemide or vancomycin.

that the decreased glomerular filtration rate seen with semistarvation may increase serum levels of the drug and thereby lead to ototoxicity.

Noise has been shown to potentiate the auditory toxicity of the aminoglycosides. In the cochlea, Brown and associates (1980) using kanamycin and Jauhiainen and colleagues (1972) using neomycin found the number of hair cells lost by subjecting guinea pigs simultaneously to both noise and kanamycin far outstripped the sum of the two agents when used alone. Since Hawkins (1971) has shown that noise causes vascular changes which induce hair cell ischemia, Brown and coworkers (1980) suggested that noise renders the cells more vulnerable to the effects of aminoglycosides. Noise, however, had no effect on the pharmacokinetics of kanamycin, and it has never been shown to be a factor in vestibular toxicity.

Finally, observing that preweanling mice exposed to elevated temperatures suffered from increased aminoglycoside ototoxicity as measured by electrocochleography, Henry and associates (1983) speculated that fever might also be a risk factor in humans. They postulated that increased metabolic demands from hyperthermia could leave the hair cells more vulnerable, and they suggested that noise and even hyperthyroidism might work in the same fashion. They attempted to control for dehydration with daily weighings and injections of dilute solutions of aminoglycosides. Nevertheless, dehydration may also have played a role. They did not examine the vestibular apparatus.

ELDERLY

The elderly are a unique population when it comes to pharmacotherapeutics, and many authors have speculated that they might have an increased risk of vestibular damage (Edson & Terrell, 1987; Lampe, 1986; Appel & Neu, 1978; Nordstrom et al., 1973; and Tjernstrom et al, 1973). Studies on vestibular toxicity among elderly patients, however, have not confirmed this speculation (Fee, 1980; Lane et al., 1977; Lerner et al., 1977; Neu & Bendush, 1976; Nordstrom et al., 1973; and Finegold et al., 1958). One reason for the negative research findings is the low incidence rate and low power of some of the studies. Jackson & Arcieri (1971) reviewed 70 of the 72 cases of ototoxicity that occurred during the gentamicin clinical trials from 1962-1969 and found the effect to be variable. Overall, there was no age difference between those with and without ototoxicity. However, patients with renal insufficiency and toxicity were younger. While not statistically significant, patients with normal kidneys and ototoxicity were older.

Speculation about a possibly increased risk comes about for a variety of reasons. First of all, the aged have a higher incidence of adverse drug reactions (Hurwitz, 1969). This may be due to inadequate compliance with instructions, the presence of multiple diseases, and polypharmacy (Ljungberg & Nilsson-Ehle, 1987). Secondly, they seem to have a heightened sensitivity to certain drugs independent of serum concentration (Gordon & Preiksaitis, 1988; Castledon et al., 1977). Finally, a host of changes take place in the aging body which may alter the pharmacokinetics of therapeutic agents (Ljungberg & Nilsson-Ehle, 1987 & Schmucker, 1984).

Of those which have an impact on aminoglycoside distribution, fluid shifts secondary to hemodynamic instability are frequently seen in critically ill surgical patients, many of whom are elderly (Dasta et al., 1988). Moreover, the elderly might theoretically have a smaller volume of distribution for water-soluble drugs, such as the aminoglycosides, due to a decrease in lean muscle mass and an increase in fat. For example, the percentage of body fat can increase from 18 to 36% in men and from 33 to 48% in women (Greenblatt et al., 1982). This means that the same dose which produces appropriate levels in a 40-year-old may cause an overdose in a patient over the age of 70 with the same weight. Furthermore, the aging kidney suffers a 1-2% per year decline in blood flow, an eventual 50% reduction in glomerular filtration rate, a loss of functioning nephrons, a decrease in secretory/absorptive capacity, and a high incidence of spontaneous glomerular sclerosis (Schmucker, 1984).

This decline in renal function can dramatically increase the half-life of substances, such as the aminoglycosides, which are renally eliminated, and it is of paramount importance (Vartia & Leikola, 1960). In fact, when controlled for renal function, hematocrit, fever, penicillin usage, and percentage of ideal body weight, Bauer & Blouin (1983) found that neither clearance, half-life, nor volume of distribution of gentamicin, tobramycin, or amikacin varied with age. Not only does this run counter to the notion that they would have a lower volume of distribution due to loss of lean body mass, but it also suggests that renal status and not age per se is the critical factor.

In their review of the literature, Kjungberg & Nilsson-Ehle (1987) concluded that as a group, based on available data, the elderly had no

substantial reduction in metabolism or absorption of pharmacological agents. There is, however, substantial individual variation. The literature, unfortunately, is very sparse, and there may be other age-related factors which influence the pharmacokinetics of the aminoglycosides in ways which have yet to be elucidated. It is certainly difficult to perform adequately controlled studies due to the large number of variables such as multiple disease states, polypharmacy, and variations in activity levels which must be addressed.

If the elderly do have an increased incidence, the question still remains as to why the aminoglycosides might preferentially affect the elderly. One possibility is that the 20-40% decrease in the number of vestibular hair cells associated with aging (Rosenhall, 1973) might simply leave elderly patients with fewer cells to lose before they become symptomatic. This is consistent with observations that patients treated with previous doses of aminoglycosides and patients with preexisting auditory impairment suffer from increased risk of vestibular toxicity (Gilman et al., 1985; and Wilson et al., 1984). Like the elderly, these patients might be expected to have fewer hair cells to lose before becoming symptomatic. Other researchers have speculated that chronic diseases and poor appetite may reduce some elderly patients to a state of semistarvation which they found to be one of the risk factors (Prazma et al., 1983). Renal disease might also contribute. Creatinine clearance measurements are flawed because tubular secretion of creatinine causes overestimation of glomerular filtration rate (GFR), and this effect worsens in cases of declining GFR such as are seen in the aged (Kim et al., 1969). This may cause clinicians to overestimate renal function and administer more toxic

doses. Moreover, the replacement of lean body mass with adipose tissue seen in aging leads to a decrease in creatinine production which further complicates calculations (Greenblatt et al., 1982). Finally, as Fowler (1947) pointed out, elderly patients are less able to compensate for aminoglycoside-induced vestibular damage and might present themselves earlier. In that sense, the elderly, with their impaired ability to compensate for vestibular damage, are a unique population ideally suited for studying vestibular toxicity.

FUTURE USAGE

The question of whether the elderly are at increased risk is a significant one, and it is intimately related to the debate over the aminoglycosides' place in current clinical practice. The three important considerations are side-effects, economics, and efficacy. The side effects have already been discussed, and their economic implications are magnified when examined in the setting of an elderly population.

Those over the age of 65 currently make up 12% of the 251 million people in this country. By 2030 their ranks will swell to 21% of 317 million people (Waldo et al., 1989). Since they disproportionately consumed 36% of the $447 billion health care dollars spent last year, their physical health has a major impact on the economic health of the country both now and in the future. The monetary and human costs of an increase in dizziness among elderly patients therefore becomes significant. Dizziness and balance abnormalities are important risk factors in predicting the likelihood of falling (Tinetti et al., 1988; Tinetti et al., 1986). Roughly 30% of community-living

persons over the age of 65 are estimated to fall each year, and many of these falls are dizziness-related (Prudham & Evans, 1981). The decreased bone density seen with osteoporosis can transform a relatively minor fall into the tragedy of a hip fracture which carries a 15-30% one-year mortality rate in patients over the age of 60 (Kenzora, 1984). The economic cost is staggering, with the 1980 total annual cost of new hip fractures estimated at $2 billion (unpublished paper quoted in Baker & Harvey, 1985).

There are other costs involved as well. Compared to some of the newer agents designed to replace them, the acquisition cost of aminoglycosides appears cheap at first glance. Since aminoglycosides are often used in combination with other agents, the added acquisition cost of using other agents must be added as well. Moreover, Eisenberg (1987) found that the cost of an individual patient with an episode of nephrotoxicity is $2,501 to the hospital and $5,376 to the third party payer. Therefore, the additional cost to the hospital per course of therapy, distributed among all patients using aminoglycosides, is $183 per patient. Furthermore, there is an additional cost of routinely monitoring drug serum levels, BUN, and serum creatinine that would not be incurred if safer antibiotics were used. This cost can range from $75-200 per patient (Sochalski et al., 1988). Finally, when compared to single agent therapy, there is also the further expense incurred by increasing the workload of nurses, pharmacists, and other staff as well as the need for more equipment such as needles, bottles, etc. (Quintiliani et al., 1986).

The third consideration in deciding the place of aminoglycosides is therapeutic effectiveness. Efforts to modify aminoglycoside molecules to

reduce the toxicity without decreasing efficacy have failed and have largely been abandoned (Pancoast, 1988). Nevertheless, new classes of antibiotics and regimens of combination therapy have arisen and have shown some promise. For many CNS infections, third generation cephalosporins are now preferable when aerobic gram-negative organisms are involved (Pancoast, 1988). Beta-lactams are also replacing aminoglycosides for abdominal and pelvic mixed infections because of their superior gram-positive and anaerobic coverage (Pancoast, 1988; Quintiliani et al., 1986). For example, a study here at Yale has demonstrated that there is no major difference between cefotetan and combination therapy which includes aminoglycosides in the treatment of a variety of anaerobic infections (Sochalski et al., 1988).

In their review of the literature, DiPiro & Bowden (1989) concluded that aztreonam was at least as effective as aminoglycosides for lower respiratory, intra-abdominal, and other infections with gram-negative organisms including *P. aeruginosa.* Ceftazidime and cefoperazone have excellent activity against *P. aeruginosa* and are being used as single agent therapy in a variety of situations (Quintiliani et al., 1986). Imipenem-cilistatin is another excellent alternative to the aminoglycosides (DiPiro & Bowden, 1989).

In summary, the aminoglycoside antibiotics can reach high concentrations with a protracted half-life in the endolymph where they are toxic to vestibular hair cells. The exact mechanism is unknown, but elderly patients may have an increased risk. This study examined this special population and attempted to determine if, indeed, the elderly are at increased

risk of vestibular damage. When the aminoglycosides were first introduced, it was felt that although they had significant side-effects, their use was justified because of their impressive clinical effect in certain infections. With the introduction of new, safer antibiotics into our clinical armamentarium, it may once again be time to reevaluate their place in current medical practice.

METHODS

A prospective observational cohort design was chosen for this study. This design is the least intrusive to both subjects and hospital staff while still allowing for effective collection of data.

SUBJECTS AND SETTING

The potential subjects in this study were all in-patients at the Yale-New Haven Hospital (New Haven, CT), the West Haven Veterans Administration Hospital (West Haven, CT), or St. Mary's Hospital (Waterbury, CT) who were discharged between August and December of 1990. These facilities are, respectively, a university hospital, a veterans hospital, and a community hospital. Both male and female community-living and nursing home residents over the age of 65 were included.

The study (exposed) group comprised those who were treated with an intravenous antibiotic course which included at least five days of any aminoglycoside. The control (unexposed) group had at least a five day course of antibiotics in which one of the control drugs was used. Since aminoglycosides are used predominantly for *Pseudomonas* coverage, beta-lactam antibiotics such as aztreonam, imipenem, ceftazidime, or one of the anti-*Pseudomonas* penicillin (azlocillin, mezlocillin, carbenicillin, ticarcillin, or piperacillin) were selected as the control drugs due to their similar spectrum. Subjects who received more than one course of IV antibiotics during their hospitalization were included, but if they received aminoglycosides, they were

placed in the "exposed" group. Antibiotics administered topically, as eyedrops, or via bladder irrigation were ignored since their systemic effects would be minimal.

An effort was made to include a broad a spectrum of subjects to make the results as generalizable as possible. Subjects were excluded, however, if they had preexisting severe renal disease (serum creatinine >3.5) or were hospitalized more than four months because it would have greatly complicated interpretation of results. Additionally, those subjects who were rehospitalized between the time of the index hospitalization and the time of the telephone interview were excluded. For practical purposes, subjects who were deaf, mute, or cognitively impaired (unable to provide accurate answers to survey questions), could not be contacted by telephone, or were in hospice at the time of the telephone interview were likewise excluded from the study.

The names of potential subjects were obtained from lists provided by the hospital pharmacies or medical information services [Table 3]. The printouts from each hospital differed as to the screening criteria. The pharmacy printout from St.Mary's listed 174 names of those who were at least 65 years old and who had at least one order for one of the study antibiotics. Examination of the pharmacy computer eliminated 114 persons due to an insufficient length of antibiotic use. The charts for the remaining 60 patients were then requested and examined.

The Yale-New Haven Hospital printout provided 307 names of persons at least 65 years old along with a list of their antibiotic start and stop dates. Charts for the 178 persons who had a sufficient course of antibiotics were

TABLE 3

SOURCE OF STUDY POPULATION

HOSPITAL	PHARMACY LIST	CHARTS REQUESTED	CHARTS RECEIVED	SUBJECTS USED
St. Mary's	174	60	60	5
YNHH	307	178	108	20
WHVAH	*	107	79	17
Total		345	247	42

*Uncountable.

Pharmacy list = list of potential subjects generated by pharmacy computer.

Charts requested = subjects from printout who meet the criteria for age and antibiotic length as determined by the pharmacy computer.

Charts received = the number of charts requested which were received from medical records.

Subjects used = the number of subjects meeting the study criteria who were included in the data analysis.

requested. Unfortunately, the hospital policy does not allow incomplete charts to be used for research purposes. Seventy charts remained incomplete eight weeks after discharge and could therefore not be used in the study.

The Veterans Hospital printout was essentially a list of orders placed to the pharmacy for stock items. The total number of subjects was uncountable since it listed all age groups, included multiple listings for each patient, was not alphabetized, and included requests for sterile saline, multivitamins, and other items which were not part of the study. Using the pharmacy computer, however, it was possible to pare the number of potential subjects who were 65 or older and had received a sufficient course of antibiotics down to 79. Unfortunately, it was not possible to determine from the computer if all these subjects had been discharged or were still in the hospital. By the end of the pilot study 28 charts from the WHVAH were not available because the subjects were still in the hospital.

There was only one refusal (an unexposed patient from YNHH) to participate in the study. Medical record data from this person were not included in the data analysis. Of those included in the study, five subjects came St. Mary's, twenty came from YNHH, and seventeen came from the WHVAH.

DATA

Once the charts were received, all demographic data, past medical history, hospital course, medications, infecting organisms, surgical procedures, allergies, lab data, vital signs, length of hospitalization and antibiotic usage

were extracted from the medical record. Those subjects who met the inclusion criteria were contacted by telephone.

Since the onset of vestibular toxicity can sometimes occur several weeks after discontinuation of the antibiotic (Neu & Bendush, 1976), the subjects were contacted by telephone two to eight weeks after their discharge to avoid missing any cases. This waiting period also allowed subjects to equilibrate in their home environment subsequent to their hospitalization. It was felt that increasing the time of contact beyond eight weeks after discharge could result in an increase in recall bias by the subjects. After informed consent was obtained, the subjects were asked if they had dizziness, what type they had, how severe it was, if they had a diagnosis for it, what medications they take for it, when it began, what brings it on, when was the most recent episode, and if they have had dizziness-related accidents. An effort was made to identify those cases in which dizziness could be attributed to known causes. Subjects were also asked about vision, hearing, and alcohol use.

Although the author performed both the chart extraction and the telephone interview, these were done in batches to decrease the likelihood that knowledge of the antibiotic regimen would influence the interviewer. Hospital treatment was not discussed on the telephone.

DEFINITION OF VARIABLES

Renal insufficiency was estimated using BUN (nl=8-18 mg/dl) and creatinine (nl=0.5-1.2 mg/dl). Nutritional status was estimated using albumin (nl=3.5-5.0). Data on liver dysfunction were taken from the admission history

and physical and the discharge summary and based on the presence of cirrhosis or ascites. The most abnormal lab values from each subject throughout the admission were compiled to calculate a score on the standard APACHE II (Acute Physiology and Chronic Health Evaluation) Severity of Disease Classification System. Although Knaus et al. (1985) developed this scale as a predictor of hospital mortality in ICU patients, they suggested that it could also be used in research protocols to compare severity of disease between the exposed and unexposed groups.

For the purpose of this study, dizziness was defined as a complaint of lightheadedness, disequilibrium, vertigo, or other ill-defined sensations of motion. "New-onset dizziness" was defined as dizziness that could not be ascribed to any other known process and which had begun since the hospitalization. "Increased severity" or "increased frequency" of dizziness since the hospitalization were based on the subjects' subjective opinions. Those with new-onset dizziness were automatically considered to have both an increased severity and frequency of dizziness. A subject was considered to have "worsened dizziness" if he or she complained of either new-onset dizziness, an increase in the severity of dizziness, or an increase in the frequency of dizziness episodes.

Assessment of post-hospitalization activity levels was based on a modified life-space diameter in which subjects were segregated according to their ability to get out of bed, leave the home, and leave the home without assistance (May et al, 1985). Those who left their home were asked to quantitate the number of blocks they felt they could walk on a given day.

Finally, obesity was estimated using self-reported height and weight to compute a body mass index (BMI), which is the weight in kilograms divided by the square of the height in meters (Stavig et al., 1984).

STATISTICAL ANALYSIS

Data were stored on an Optima 386SX personal computer, and statistical analyses were carried out using a standard statistical package (SAS Institute Inc. Cary, NC, 1987). Chi square analyses were used to analyze dichotomous data which had at least five items in each cell. The remainder of the dichotomous data were analyzed using the Fisher exact test. Student's T-tests were used to analyze dimensional data [Table 4].

TABLE 4

DATA SOURCES AND STATISTICS

DATA	SOURCE	STATISTICS
gender	chart	chi square
race	chart	Fisher exact
diuretic usage	chart	chi square
maximum BUN	chart	Student's T-test
maximum creatinine	chart	Student's T-test
last hematocrit	chart	Student's T-test
last systolic blood pressure	chart	Student's T-test
last diastolic blood pressure	chart	Student's T-test
maximum temperature	chart	Student's T-test
APACHE II score	chart	Student's T-test
length of hospitalization	chart	Student's T-test
had surgery	chart	chi square
EtOH use #1	chart	Fisher exact
EtOH use #2	interview	Fisher exact
dizziness present	interview	Fisher exact
new-onset dizziness	interview	Fisher exact
increased frequency of dizziness	interview	Fisher exact
increased severity of dizziness	interview	Fisher exact
worsened dizziness*	interview	Fisher exact
bedridden	interview	Fisher exact
housebound	interview	Fisher exact
leaves house alone	interview	chi square
blocks walked	interview	Student's T-test
body mass index (BMI)	interview	Student's T-test
hearing	interview	Fisher exact

*Worsened dizziness = report of new-onset dizziness or an increase in frequency or severity of dizziness.

RESULTS

The average age (+/-SD) of the 42 subjects was 73.5 (+/- 6.23). Twenty four (57%) were male and 18 were female (43%). Thirty-five (83%) 1were white, three (7%) were black, and 4 (10%) did not have their race listed in the chart.

There were 26 (62%) unexposed and 16 (38%) exposed subjects. Although the study was open to all persons with five or more days of treatment with any aminoglycoside, in actual fact the exposed group is only made up of subjects who received gentamicin. This probably reflects the local pattern of antibiotic prescription. Among the unexposed subjects, 15 received cefoperazone, 4 received ceftazidime, 3 received ticarcillin, and 4 received mezlocillin as their primary antibiotic [Table 5]. Again, all the control drugs were not represented.

Of the 42 subjects, 10 (63%) of the exposed and 14 (54%) of the unexposed subjects were males, and there was no statistically significant difference in gender distribution between the populations by chi square ($p = 0.58$). Fourteen (88%) exposed and 21 (81%) unexposed subjects were white. Two (12%) exposed and one (4%) unexposed subject were black. There was no statistically significant racial difference between the exposed and unexposed subjects by Fisher exact test (white: $p = 0.69$, black: $p = 0.55$). Four of the unexposed subjects did not have their race listed in the chart. The distribution of subjects having surgery during the admission in question was also not statistically significant by chi square ($p = 0.74$)[Table 6].

TABLE 5

PRIMARY ANTIBIOTIC USED

ANTIBIOTIC	# OF SUBJECTS (%)
gentamicin	16 (38%)
cefoperazone	15 (36%)
ceftazidime	4 (9.5%)
mezlocillin	4 (9.5%)
ticarcillin	3 (7.0%)

The populations were compared using a student's T test for age, maximum BUN, maximum creatinine, minimum albumin, last hematocrit, maximum temperature, last blood pressure, length of hospitalization, and body mass index. The Student's T test was also used to compare self-reported activity levels (in blocks walked per day) and APACHE II scores. None of these variables were found to be statistically significant except length of hospitalization [Table 7]. Unexposed subjects remained in the hospital for 25 (+/-17) days compared to exposed subjects who were hospitalized only 15 (+/-12) days ($p = 0.036$).

When the exposed and unexposed subjects were compared by Fisher exact test for activity levels, there was no statistically significant difference in

TABLE 6
COMPARISON OF EXPOSED AND UNEXPOSED SUBJECTS
NOMINAL DATA

VARIABLE	EXPOSED (n=16)	UNEXPOSED (n=26)	p=
gender			
male	10 (63%)	14 (54%)	0.58 §
female	6 (37%)	12 (46%)	
race			
white	14 (88%)	21 (81%)	0.69 ¶
black	2 (12%)	1 (4%)	0.55 ¶
unlisted	0 (0%)	4 (15%)	
surgery			
yes	9 (56%)	16 (62%)	0.74 §
no	7 (44%)	10 (38%)	
bedridden			
yes	0 (0%)	1 (4%)	1.0 ¶
no	16 (100%)	25 (96%)	
housebound			
yes	1 (6%)	4 (16%)	0.63 ¶
no	15 (94%)	21 (80%)	
refused to answer	0 (0%)	1 (4%)	
can leave home alone			
yes	9 (56%)	16 (64%)	0.62 §
no	7 (44%)	9 (32%)	
refused to answer	0 (0%)	1 (4%)	
alcohol use #1*			
more than social	3 (38%)	3 (15%)	0.31 ¶
none or social	13 (62%)	17 (62%)	
unlisted	8 (50%)	6 (23%)	
alcohol use #2*			
more than social	5 (31%)	3 (12%)	0.23 ¶
none or social	11 (69%)	22 (84%)	
refused	0 (0%)	1 (4%)	
hearing**			
good	13 (81%)	23 (88%)	0.66 ¶
poor	3 (19%)	3 (12%)	
diuretics			
used	6 (38%)	17 (68%)	0.044 §
not used	10 (62%)	9 (32%)	

* = Alcohol use greater than "social" use or at least once per day. Variable #1 is obtained from the chart and #2 is obtained during the survey.
** = Subject can hear a friend talking in room.
¶ = Fisher exact test
§ = chi square

Table 7
COMPARISON OF EXPOSED AND UNEXPOSED SUBJECTS DIMENSIONAL DATA

VARIABLE	TEST	EXPOSED	UNEXPOSED	p=
Age	range	65-88	66-86	
	mean (+/- SD)	75.7 (6.7)	72.1 (6.1)	0.086
BUN	range	10-91	13-80	
	mean (+/- SD)	31.4 (19.8)	29.8 (17.8)	0.79
Creatinine	range	1.0-3.4	0.7-2.8	
	mean (+/- SD)	1.79 (0.68)	1.48 (0.54)	0.12
Albumin	range	2.1-4.2	1.0-4.9	
	mean (+/- SD)	2.92 (0.67)	2.84 (0.92)	0.81
Hematocrit	range	30-43	26-45	
	mean (+/- SD)	34.9 (3.6)	35.0 (5.2)	0.95
Temperature	range	98.8-106.6	98.8-103.8	
	mean (+/- SD)	101.8 (2.1)	101.3 (1.4)	0.29
Systolic BP	range	100-160	110-175	
	mean (+/- SD)	127.5 (16)	130.9 (18)	0.54
Diastolic BP	range	60-90	56-100	
	mean (+/- SD)	71.9 (10)	71.6 (11)	0.93
Length of Hospital Stay	range	6-53	6-68	
	mean (+/- SD)	15.0 (12)	25.4 (17)	0.036
Body Mass Index	range	16.9-31.4	16.2-40.0	
	mean (+/- SD)	25.3 (4.5)	25.1 (6.5)	0.94
APACHE II	range	5-43	6-39	
	mean (+/- SD)	15.9 (9.9)	17.5 (8.5)	0.59
Activity level*	range	0-12	0-6	
	mean (+/- SD)	2.9 (3.1)	1.5 (1.5)	0.051

*Activity level is the reported number of blocks the subject can walk per day.

p values calculated using a Student's T-test.

the distributions of those who were bed-ridden or house-bound (p values 1.0 and 0.63 respectively). When asked if they could leave their home without assistance, 9 (56%) exposed and 16 (64%) unexposed answered in the affirmative. There was no statistically significant difference between the populations by chi square test for this variable ($p = 0.62$).

As a crude measure of visual acuity, subjects were asked if they could see well enough to recognize a friend across the room. All subjects answered in the affirmative. To assess hearing, subjects were asked if they could hear a friend talking to them from across the room. Thirteen (81%) exposed and 23 (88%) unexposed subjects felt they could do so. There was no significant difference between the populations by Fisher exact test ($p = 0.66$). When liver function was examined, it was noted that one unexposed subject had hepatitis of unknown etiology and one had cirrhosis (2/26, 7.7%). Only one (6.2%) exposed subject had liver pathology. In this case it was alcoholic hepatitis. The small number of subjects with liver disease makes it difficult to do statistical analysis, but the incidences appear similar.

Although not statistically significant by Fisher exact test, alcohol use seemed to be higher in the exposed population than the unexposed population. This was true both for data obtained from the chart ($p = 0.31$) and data obtained over the ($p = 0.23$). There was a 78% agreement between the chart information and the telephone survey for this variable. A kappa of 0.27 showed that there was poor agreement between the two reports of alcohol use. The difference between the populations for diuretic usage was statistically significant by chi square. Only 6 (38%) of exposed subjects received diuretics while 18 (69%) of unexposed subjects received them ($p = 0.044$).

ASSESSMENT OF DIZZINESS

Subjective reports of dizziness were assessed in the telephone interview. Five (31%) subjects reported experiencing episodes of feeling dizzy, lightheaded, or faint. Seven (27%) unexposed subjects in the exposed group reported these symptoms (p= 1.0)[Table 8]. For the question "Did you have this [dizziness] prior to your hospitalization?" 12.5% (2) of the exposed subjects as compared to 7.7% (2) of the unexposed subjects answered affirmatively (p = 0.63). When questioned as to an increase in the frequency of dizziness episodes since their hospitalization, two exposed (13%) and three (11.5%) unexposed subjects felt there was an increase (p = 1.0). A full 18.8% (3) of the exposed subjects reported an increase in the severity of dizziness compared to only 8.0% (2) of the unexposed subjects, but again this was not statistically significant by Fisher exact test (p = 0.36). Finally, when subjects reporting new-onset dizziness or an increase in severity or frequency of episodes were grouped together under the category of worsened dizziness, 18.8% of the exposed (3) and 11.5% (3) of the unexposed subjects had worsened dizziness since their hospitalization (Fisher exact p = 0.66). Based on these percentages, the relative risk of worsened dizziness for elderly patients after receiving at least five days of aminoglycoside therapy is 1.09 (95% confidence interval: 0.152-16.98).

Of those who reported dizziness, two unexposed subjects and no exposed subjects suffered a fall between their discharge and the telephone call. One subject fell five times and reported dizziness prior to some of the falls. The other subject fell once and was not dizzy at the time.

There were differences in the exposed and unexposed populations for four variables (age, length of hospitalization, diuretic use, and the number of blocks the subjects could walk) which were either statistically significant or close to it. Each variable was made binary. Age was divided into an older cohort (over 74 years old)

and a younger cohort (74 and under). Length of hospitalization was stratified into those hospitalized for 20 days or more and those hospitalized for less. The number of blocks walked was divided into two or less and three or more. Diuretic usage was already a binary variable. Table 9 presents the number of subjects and the percentages in each group. The sample size was not large enough to perform the Mantel-Haenszel chi square or relative risk.

Diuretic usage was seen in 1 (17%) exposed and 2 (11%) unexposed subjects who reported worsened dizziness. Three (33%) of the exposed and only 1 (13%) unexposed subjects were 74 years old or older. A hospitalization of 20 or more days was seen in 2 (67%) of the exposed and 2 (15%) of the unexposed subjects who reported worsened dizziness. Finally, worsened dizziness was reported in 2 (25%) exposed and 1 (25%) unexposed subjects who walked 3 or more blocks.

TABLE 8

COMPARISON OF EXPOSED AND UNEXPOSED SUBJECTS DIZZINESS OUTCOME

VARIABLE	EXPOSED n = 16	UNEXPOSED n = 26	p=
dizziness (new or old)			
present	5 (31%)	7 (27%)	1.0
absent	11 (69%)	19 (73%)	
new-onset dizziness			
present	2 (13%)	2 (8%)	0.63
absent	14 (87%)	24 (92%)	
dizziness frequency			
increased	2 (13%)	3 (12%)	1.0
decreased or unchanged	13 (81%)	23 (88%)	
refused to answer	1 (6%)	0 (0%)	
dizziness severity			
increased	3 (19%)	2 (8%)	0.36
decreased or unchanged	13 (81%)	23 (88%)	
refused to answer	0 (0%)	1 (4%)	
worsened dizziness			
present	3 (19%)	3 (12%)	0.66
absent	13 (81%)	23 (88%)	

p values calculated using Fisher exact test.

New-onset dizziness = reports of dizziness which was not present prior to hospitalization.

Worsened dizziness = reports of either new-onset dizziness or an increase in frequency or severity of dizziness.

TABLE 9

STRATIFICATION OF WORSENED DIZZINESS* BY POTENTIAL CONFOUNDING VARIABLES

VARIABLE	SUBJECTS REPORTING WORSENED DIZZINESS	
	EXPOSED (%)	UNEXPOSED (%)
	n = 16	n = 26
Diuretic use		
yes (n=24)	1/6 (17%)	2/18 (11%)
no (n=18)	2/10 (20%)	1/8 (13%)
Age over 73 years old		
yes (n=17)	3/9 (33%)	1/8 (13%)
no (n=25)	0/7 (0%)	2/18 (11%)
Hospitalization		
20 or more days (n=17)	2/3 (67%)	2/13 (15%)
less than 20 days (n=25)	1/13 (8%)	1/13 (8%)
Blocks walked		
3 or more (n=12)	2/8 (25%)	1/4 (25%)
less than 3 (n=30)	1/8 (13%)	2/22 (9%)

*Worsened dizziness= reports of either new-onset dizziness or an increase in the frequency or severity of dizziness episodes.

DISCUSSION

Elderly subjects who received in-hospital aminoglycosides and elderly subjects who did not receive these agents were compared for subjective reporting of dizziness. This pilot study demonstrated a trend in which the aminoglycoside-exposed population subjectively reported a higher rate of new-onset dizziness, worsened dizziness, or increased severity of dizziness than those who had not received them. This trend shows a 5-11% higher incidence of symptoms in those who received aminoglycosides, and it is larger than the 2-2.5% range of historical controls for gentamicin toxicity (Jackson & Arcieri, 1971; Arcieri et al., 1970). This suggests that elderly patients may have an increased risk of aminoglycoside-induced dizziness.

It is possible that this population differs from the populations studied in the other protocols in some significant way other than age. Moreover, the trend was not statistically significant, so the small sample size did not permit a more definitive conclusion. If the elderly do not actually have an increased risk of dizziness, there are many reasons why a trend could have artifactually been found. First, the choice of antibiotic, and hence the separation into exposed and unexposed groups, was not randomized or even controlled by the investigators. This could lead to a susceptibility bias (Horwitz et al., 1985) since the reasons for administering (or not administering) aminoglycosides could somehow be related to a predisposition to vestibular toxicity. For example, since clinicians who felt that subjects had a high risk for aminoglycoside-induced side-effects would be less likely to use these agents, one would expect to find less dizziness in the exposed group.

Secondly, the observed trend could also result from unmeasured differences between the exposed and unexposed populations. No statistically significant differences, however, were found between the populations for variables such as age, gender, race, various lab values, occurrence of surgery during the admission, hearing, vision, or level of activity. Commonly cited risk factors for aminoglycoside vestibular toxicity such as renal insufficiency, obesity, liver dysfunction, starvation, and peak temperature were surveyed, and no statistically significant difference between the populations were noted. Severity of illness was assessed using APACHE II scores, and although unexposed subjects were hospitalized longer, there was no statistically significant difference between the two populations. Maximum BUN and creatinine were used as a crude measure of hydration status. The hospital charts did not contain sufficient information to examine preexisting auditory impairment or the effects of noise on these patients. Moreover, since all patients did not have blood culture results, it was not possible to accurately assess bacteremia. Finally, since serum levels of the beta-lactams are not routinely measured, it was not possible to compare the populations for possible overdosage of antibiotics.

Nevertheless, there were some significant differences between the two study populations. When the dizziness outcomes were stratified by these variables, exposed subjects still had a higher percentage of reports of worsened dizziness than unexposed subjects in both diuretic groups, the older age group, the longer hospitalization group, and the less active group. Exposed and unexposed subjects were equal in their reporting of worsened dizziness in the

most active group and the short hospitalization group, but a higher percentage of the exposed population came from these two groups. By having a higher percentage of the exposed subjects in subpopulations where there was no difference between exposed and unexposed subjects in terms of worsened dizziness, the overall magnitude of the difference between the exposed and unexposed subjects would therefore be lower. There were more reports of dizziness among unexposed subjects in the younger age group than among the exposed subjects. Since 69% of the unexposed subjects were younger while only 44% of the exposed subjects were younger, this would increase the incidence of dizziness seen in the unexposed group. Thus the net effect of the latter three confounding variables seems to be to decrease the observed trend. Although proper statistics were not done because of the sample size, taken together the results indicate that older subjects who were less active and had longer hospitalizations had a higher incidence of dizziness when given aminoglycoside antibiotics.

The sample size was the greatest limitation of the study. Given the breadth of the information collected in this study, it would have been very interesting to use a variety of other statistical tests, such as multivariant analysis, on the data. This was not possible due to the small sample size. Additional subjects would also be needed to compare the populations for occurrence of specific types of concurrent medical problems, surgical procedures, and medications. Another limitation of the study was that only a small percentage of the potential population was utilized. Although efforts were made to include a broad a spectrum of subjects, a large number of

subjects were unavoidably excluded due to restrictions on the review of medical charts.

Based on the current sample size, the power of this study to demonstrate at the 5% level a difference the magnitude of the observed trend is very small. Assuming the frequencies noted in this study are the actual frequencies which would be seen if the entire population over the age of 65 was sampled, the sample size needed to increase the power to 85% at an alpha of 5% would be roughly 250 subjects in each arm for a total of 500 subjects. Using the maximum rate of data collection, it would require approximately three years to complete the study.

If this pilot study had detected an actual difference secondary to aminoglycoside use, it could be due to the myriad of pharmacokinetic changes inherent in aging. Bauer & Blouin's (1983) work, though, suggests that these changes do not apply to aminoglycosides. More likely, aminoglycoside usage takes its toll on the vestibular hair cell population in all patients regardless of age even if given subtherapeutically in a manner similar to the effect on rat kidneys seen by Houghton et al. (1988). Therefore, the age-associated decline in the number of vestibular hair cells observed by Rosenhall (1973) and an inability to adequately compensate for their loss simply leaves elderly patients with fewer hair cells to lose before they become symptomatic.

Clearly, more work needs to be done in this area. Since many of the other studies used the relatively insensitive thermal test as a determination of whether toxicity existed, it is possible that they missed the more subtle differences, such as the increase in severity of dizziness, which were seen with

the telephone survey. The advantage of the thermal test is that it provides more objective data than the telephone survey. Future studies might benefit from integrating both approaches into the protocol. Although only gentamicin was actually used, this study also attempted to examine all the aminoglycosides as a group. By specifically focusing on gentamicin, which has a higher rate of vestibular toxicity, future studies would require fewer subjects to demonstrate a difference between the study groups.

Despite the length of time required, the trend indicates it is useful to pursue this line of research. An increase in dizziness symptoms in a geriatric population would be clinically significant. Dizziness can lead to falls and to the tragedy of a hip fracture. Although only two subjects fell during the brief tenure of this study, one would expect that the number of falls would increase as the subjects recuperated from their hospitalizations and became more active. Those with dizziness or balance abnormalities might also be expected to fall more frequently. Continuation of the study might settle the debate over the possibility of increased risk among geriatric patients, and through more careful antibiotic use, might decrease the incidence of life-threatening hip fractures and other injuries.

SUMMARY

The significant toxicities of the aminoglycosides are well-recognized, and vestibular toxicity is already known to be one of them. This study focused on the question of whether the elderly are at an increased risk of aminoglycoside-induced vestibular damage. Subjects who were exposed to aminoglycosides

and those who were unexposed were compared for subjective reporting of dizziness. Those subjects exposed to aminoglycosides reported a higher incidence of dizziness symptoms than both the unexposed subjects and the historical controls. Although the results were not statistically significant, it suggests that the elderly may have an increased risk of dizziness with aminoglycoside use.

The failure of this study to conclusively demonstrate a higher incidence may in part be due to the study's low power. Continuation of this study, therefore, may offer a more complete understanding of this economically important problem. Given the aminoglycosides' incredible clinical success, it may not yet be possible to substitute them for other antibiotics. Nevertheless, their known toxicities should imbue clinicians with a healthy sense of caution when prescribing them and a strong desire to someday find a replacement.

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